



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
---------------	-------------	----------------------	---------------------

07/652,978 02/08/91 BUHR

C 4610-0027

EXAMINER

KUNZ, G

ART UNIT

PAPER NUMBER

17

18N1/0809

NANCY JOYCE GRACEY  
MORRISON & FOERSTER  
755 PAGE MILL ROAD  
PALO ALTO, CA 94304-1018

1803

DATE MAILED:

08/09/93

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/26/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- ☒ Notice of References Cited by Examiner, PTO-892.
- ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
- ☒ Notice of Art Cited by Applicant, PTO-1449.
- ☐ Notice of Informal Patent Application, PTO-152.
- ☐ Information on How to Effect Drawing Changes, PTO-1474.
- ☐

Part II SUMMARY OF ACTION

1. ☒ Claims 7-18, 20, 22 AND 27-42 are pending in the application.

Of the above, claims — are withdrawn from consideration.

2. ☒ Claims 1-6, 19, 21 AND 23-26 have been cancelled.

3. ☐ Claims — are allowed.

4. ☒ Claims 7-18, 20, 22, AND 27-42 are rejected.

5. ☐ Claims — are objected to.

6. ☐ Claims — are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on —. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on —, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed —, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. —; filed on —.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

07/652,978  
PTOL-326 (Rev. 2/83)

EXAMINER'S ACTION

Applicant's Amendment A filed April 26, 1993, in response to the Office action mailed November 11, 1992 (Paper No. 11) is acknowledged and has been entered into the record.

Claims 7 - 18, 20, 22, and 27 - 42 are pending in the case. All claims drawn to the non-elected invention have been canceled.

The amendment of claim 7 has overcome the rejection under 35 USC 102(b) as being anticipated by Padyukova et al.

The rejection of claims 8 - 9 , 11 - 12, 14 - 16, and 18 under 35 USC 103 as obvious over Robins et al. or Balzarini et al. or Ranganathan or Martin et al. in view of Khorlin et al. has been withdrawn in favor of the new obviousness rejection presented below.

The rejection of claims 20 and 22 under 35 USC 103 as being obvious over Padyukova et al. has been withdrawn in favor of the new obviousness rejection presented below.

The withdrawal of the above obviousness rejections is due to applicant's persuasive arguments that the Khorlin et al. reference does not methylene phosphonates as defined by the claims.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that

the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 7 -18, 20, 22, and 27 - 42 are rejected under 35 USC 103 as being unpatentable over Martin et al. (J. Med. Chem. 33: 2137 - 2145, 1990) or Robins et al. (J. Org. Chem. 39: 1564-1570, 1974) or Ranganathan (Tetrahedron Letters 15: 1291-1294, 1977) or Watanabe et al. (4,918,170) or Webb et al. (Nucl. Acids Res. 14: 7661-7675) or Tisdale (EP 417999) in view of Padyukova et al. (Tetrahedron Letters 28: 3623-3626, 1987) or in view of Montgomery et al. (J. Med. Chem. 22: 109 - 111, 1979).

Martin et al. discloses unphosphorylated nucleosides of claims 7, 29 and 35 - 37. Compound 2 on page 2137 is unphosphorylated 2',3'-dideoxycytosine (claims 7, 29, and 35 - 37).

Compound 3 on page 2137 is an unphosphorylated 2',3'-deoxy-2',3'-didehydrocytosine (claims 9 and 31). Compound 42 on page 2139 is unphosphorylated 2'-deoxy-2'-fluoro-(UP)thymidine (claims 10, 12, 32, 35 - 37).

Robins et al. discloses an unphosphorylated 2',3'-epoxy-nucleoside of adenosine in compound 3 on page 1565 (claims 8 and 30).

Ranganathan discloses an unphosphorylated 2'-deoxy-2'-fluoro (DOWN) adenosine (claims 10 - 11, 12 - 15, 32, and 34) and 2'-deoxy-2'-fluoro-(UP)ara-adenosine (claims 10 - 11 and 32).

5 Watanabe et al. discloses an unphosphorylated 2'-deoxy-2'-fluoro-(UP)araguanosine (column 9, Table 1 where X is OH and Y is H) (claims 10, 27, and 33).

Webb et al. discloses an unphosphorylated 2'-deoxy-N4-aziridinylcytidine on page 7662, compound v wherein R and R' are hydrogen (claims 10, 13 - 14, and 17).

10 Tisdale et al. discloses unphosphorylated 2'-deoxy-2'-fluoroguanosine and 2'-deoxy-2'-fluoro-araguanosine (claims 7, 10, 14, 27 - 28,

2'-Deoxy- adenosine, guanosine, cytidine, and uridine and thymidine are the five nucleosides that comprise DNA and  
15 RNA.

The above references teach the obviousness of the unphosphorylated 2'-dideoxy or 2',3'-dideoxy-nucleoside analogs which are generally antiviral agents.

Montgomery et al. discloses a 5'-methylene phosphonate  
20 derivative of the nucleoside analog: 5-fluoro-uridine (page 109, compound 6) and that this derivative is a potent inhibitor of thymidylate synthetase from E. coli. (page 110, column 1, paragraph 2). This compound was also cytotoxic to H.Ep.-2 cells in culture.

25 Finally, Padyukova et al. discloses 5'-methylene nucleoside

on page 3624, compounds 13 and 14. There modified nucleosides can be used for the synthesis of oligonucleotides with the expectation that such oligomers would be resistant to nucleases.

In summary, the claimed 5'-methylene nucleosides would have been obvious to the person of ordinary skill in the art at the time of the invention wanting either 1) to create 5'-nucleoside analogs that would circumvent cells resistant to the free drug cause by a lack of phosphorylating enzymes and/or 2) to incorporate said nucleoside analogs into oligonucleotides which then become resistant to nuclease digestion. Thus, the invention is prima facie obvious in the absence of clear and convincing evidence to the contrary. The examiner has established that 1) the person of ordinary skill in the art would have been able to prepare the claimed compounds and 2) that he would also have had motivation to do so. The pharmaceutical compositions of claims 20 and 35 - 37 would have also been obvious because an obvious active ingredient combined with an inert carrier has no patentable weight over the obvious active ingredient alone.

Applicant's arguments against the rejection of claims 7 - 18 and 20 and 22 under 35 USC 112, first paragraph, for the reasons already of record in the Office action mailed November 25, 1992 (Paper No. 11) have been fully considered and are deemed persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

5 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10 The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written of the invention, i.e. failing to provide an enabling description.

15 The negative proviso, "that when X is oxygen and each Y is OH, R1 at the 3'-position is hydroxyl and R1 at the 2'-position is hydrogen or hydroxyl, then B is not guanine, thymine, cytosine, uracil or adenine and when R1 at the 2'-  
20 position is hydrogen, then B is not 5-fluorouracil", inserted into claim 7 by Paper No. 14 is not supported by the disclosure.

25 Claims 7 - 18, 20, 22 and 27 - 42 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

30 Applicant has obviated the rejection of claims 7 and 11 - 13 under 35 USC, second paragraph, by the cancellation of claim 7 and the amendment of claims 11 - 13. However, the following  
35 new rejection under 35 USC 112, second paragraph, is now required because of applicant's amendment to the claims.

40 Claims 7 - 18, 20, 22, and 27 - 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing  
45 to particularly point out and distinctly claim the subject matter

which applicant regards as the invention.

Claims 7, 10, 14, 20, 38 - 42 are rendered indefinite  
because the chemical structures have been inserted into the  
claims by a separate piece of paper taped to the first sheet.  
Such glued or taped pieces of paper are unacceptable claim  
presentation. Appropriate correction is required.

The examiner has initialed and photocopied Information  
Disclosure Statements PTO Form 1449 submitted July 10, 1992  
and April 26, 1993. Once again, the references for the IDS  
submitted March 15, 1993 are still missing even though the  
applicant has resubmitted copies of said references.

No claim is allowed.

Papers related to this application may be submitted  
to Group 180 by facsimile transmission. Papers should  
be faxed to Group 180 via the PTO Fax Center located in  
Crystal Mall 1. The faxing of such papers must conform  
with the notice published in the Official Gazette, 1096  
OG 30 (November 15, 1989). The CM1 Fax Center number is  
(703) 308-4227.

Any inquiry concerning this communication or earlier  
communications from the examiner should be directed to Examiner  
Kunz whose telephone number is (703) 308-3995.

Any inquiry of a general nature or relating to the status of  
this application should be directed to the Group receptionist  
whose telephone number is (703) 308-0196.

Gary L. Kunz:glk  
July 26, 1993

*Johnnie R. Brown*  
JOHNNIE R. BROWN  
SUPERVISORY PATENT EXAMINER  
ART UNIT 183